A review of ozanimod as an emerging treatment in relapsing multiple sclerosis

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https://doi.org/10.17925/USN.2026.22.1.8

In recent decades, the therapeutic landscape for relapsing multiple sclerosis (RMS) has expanded substantially, offering patients a broad range of disease-modifying therapies with varying efficacy, safety and tolerability profiles. Ozanimod, a disease-modifying therapy approved for RMS by the U.S. Food and Drug Administration in 2020, is a selective oral sphingosine-1-phosphate (S1P) receptor modulator that has demonstrated efficacy in reducing relapse rates and magnetic resonance imaging disease activity in RMS. Within the current treatment landscape, ozanimod represents a convenient once-daily oral option with a favorable balance of efficacy and tolerability compared with earlier S1P receptor modulators. This article summarizes the relevant clinical trial data supporting the safety, efficacy and tolerability of ozanimod, as well as practical considerations, including use in special populations, concomitant medications and cost-related factors.

Keywords

Demyelinating diseases, demyelinating autoimmune diseases, CNS, disease-modifying therapies, multiple sclerosis, relapsing-remitting, pharmacology, sphingosine 1 phosphate receptor modulators

Disclosures: Asaff Harel received funds from Genentech, TG Therapeutics, Amgen, Biogen, and Sanofi to his institution outside of work on the current project. Dr Harel received funds personally from Genentech, TG Therapeutics, Amgen, Alexion and Bristol Myers Squibb outside of work on the current project. Natalie Hissong, Sadie Goodman, Isabella Henderson, Noureddin E'layan, Ayesha Rehman and Nikita Bajaj have no financial or non-financial relationships or activities to declare in relation to this article.

Acknowledgements: ChatGPT (OpenAI, San Francisco, CA, USA) was used for proofreading and language editing. OpenEvidence (OpenEvidence, Miami, FL, USA) was used to assist with identifying relevant and current literature.

Review process: Double-blind peer review.

Compliance with ethics: This article involves a review of the literature and did not involve any studies with human or animal subjects performed by any of the authors.

Data availability: Data sharing is not applicable to this article as no datasets were generated or analyzed during the writing of this article.

Authorship: All named authors meet the criteria of the International Committee of Medical Journal Editors for authorship for this manuscript, take responsibility for the integrity of the work as a whole and have given final approval for the version to be published.

Access: This article is freely accessible at touchNEUROLOGY.com. ©Touch Medical Media 2026.

Received: 9 March 2026

Accepted: 14 August 2026

Published online: 12 November 2026

Citation: *touchREVIEWS in Neurology.* 2026;22(1):Online ahead of journal publication

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Support: No funding was received in the publication of this article.

This article examines the role of ozanimod in the treatment of relapsing multiple sclerosis (RMS), summarizing relevant clinical trial data with a focus on efficacy, safety and long-term outcomes. These findings are discussed alongside practical and clinical considerations to place ozanimod within the context of the current treatment landscape.

Multiple sclerosis: Background and clinical considerations

Overview of multiple sclerosis

Multiple sclerosis (MS) is a prevalent chronic neurodegenerative disease affecting the central nervous system (CNS). MS is an immune-mediated inflammatory disease influenced by both environmental and genetic factors, resulting in demyelinating and axonal lesions in the white and gray matter of the brain and spinal cord. These lesions, the pathologic hallmark of MS, are associated with neuroaxonal damage that manifests uniquely across patients. Typically presenting in young adulthood, the initial onset of MS is often observed in patients between 20 and 40 years of age. The first clinical episode that suggests inflammatory demyelination is diagnosed as clinically isolated syndrome. For a patient to be diagnosed with MS, damage to the CNS must be disseminated in space and time, as demonstrated by additional clinical attacks, magnetic resonance imaging (MRI) findings or cerebrospinal fluid-specific oligoclonal bands.[1] The most commonly observed course of MS is characterized by short-lived and potentially reversible episodes of neurologic deficits, or relapses, which typically evolve over days to weeks. These patients are considered to have relapsing-remitting MS (RRMS). Eventually, gradual worsening of clinical disability can occur irrespective of relapses, a phenomenon referred to as secondary progressive MS. Less commonly, patients will present with primary progressive MS, in which a gradual progressive pattern of disease worsening is evident from the onset. Any of these MS typologies can be classified as active or not active based on the presence of superimposed relapses or the detection of new or worsening lesions using MRI.[2]

Patient burden and disease progression

Patients with MS face a wide range of challenges due to both the physical and cognitive symptoms associated with this disease. The availability of current disease-modifying therapies (DMTs) has demonstrated improved mobility outcomes as compared with natural history studies that demonstrate how disabling RRMS can be without intervention.[3] Prior to the use of modern DMTs, natural history studies of MS found that 50% of patients would require assistance walking, as measured by an Expanded Disability Status Scale (EDSS) score of 6 between 15 and 20 years after the onset of MS symptoms.[4–6] Recent studies show markedly improved mobility outcomes in conjunction with the use of modern DMTs. A cohort study of 517 actively managed adults with MS found that after a median of 16.8 years following MS onset, 10.7% of patients had reached an EDSS score of 6 or greater and that 20 years after onset, 16.2% of patients had an EDSS score of 6 or greater.[3] A large MSBase observational study of 14,717 adults with MS demonstrated that 13% of the DMT-treated cohort reached an EDSS score of 6 or greater within 15 years versus 41% of the untreated cohort.[7]

MS impacts patients in a variety of ways. Symptoms such as spasticity, pain, muscle weakness, fatigue, gait problems and notably balance issues can contribute to impaired mobility and increased fall risk.[8,9] Patients also experience symptoms such as mood dysregulation, sleep disturbances, bladder and bowel issues and cognitive impairment, all of which can greatly impact quality of life (QoL).[8] Fatigue is one of the most disabling symptoms of MS, affecting over 75% of patients with MS, with over 50% of patients describing it as one of the worst symptoms.[10–12] Fatigue associated with MS can negatively impact QoL and contribute to the economic burden of living with MS by limiting patients' capacity to work.[13]

Cognitive decline and memory impairment are other common challenges that patients with MS face. A recent pooled prevalence review of 5,859 participants across multiple registries and databases found that 32.5% of these patients experienced cognitive impairment, with an increase in mean disease duration and age being significant predictors of higher prevalence rates.[14] Historical comparisons emphasized slowed information processing speed as the principal cognitive impairment for patients with MS, but with the widespread use of DMTs, the cognitive processing speed among patients with MS is comparable to healthy normative expectations.[15] In the modern treatment era, the most prevalent cognitive impairment affecting patients is memory dysfunction.[15]

In addition to these major symptoms, patients with MS may also experience visual disturbances, such as double vision and optic neuritis; vertigo; sensory symptoms such as numbness or tingling; chronic pain; and psychological symptoms, including depression and anxiety.[8,16] These various symptoms collectively exacerbate the burden of MS. However, with early diagnosis and appropriate treatment, worsening of the disease and its symptoms can be managed.

Assessments of disease activity and progression

Due to the gradually worsening nature of MS and the neurodegenerative component of the disease, several measures have been used to monitor disease worsening and evaluate the level of impairment and disability in patients with MS.

Relapse rates (annualized relapse rate)

One of the primary measures classically used to assess the status of MS is the frequency of relapses, which reflects the disease's activity through fluctuations in symptoms. The most comprehensive estimates of how often relapses occur are derived from data collected during clinical trials.[17] Relapse incidence, measured by the annualized relapse rate (ARR), is a primary endpoint in many MS clinical trials because it is easy to quantify and compare among different groups.[17,18] However, ARR has limitations, including the subjective nature of relapse identification and the variability in relapse patterns over time.[19]

Disability progression (Expanded Disability Status Scale)

The EDSS is a widely used and accepted instrument for assessing worsening of disability associated with MS.[20,21] The EDSS is scored on a scale from 0.0 (normal neurologic examination) to 10.0 (death due to MS). Scores of 4.0 and 6.0 are conventionally used endpoints reflecting the onset of gait impairment and gait disability requiring assistance, respectively.[22]

Disability worsening is commonly assessed by tracking patients' EDSS scores over time. Although definitions vary across studies, confirmed disability progression (CDP) is generally defined as a ≥1.0-point increase in EDSS score sustained over 4–6 months. Time to CDP is a key efficacy endpoint in clinical trials, with more effective DMTs demonstrating lower rates of CDP or delayed progression compared with control.

Magnetic resonance imaging lesion activity

MS diagnosis necessitates the presence of lesions on MRI.[1] In addition to being a cornerstone for diagnosis, MRI has also been used to monitor disease worsening and therapeutic efficacy in clinical trials. Disease activity is indicated by the observation of new T2 lesions or enlargement of existing lesion volumes or the presence of gadolinium-enhancing (GdE) lesions.[23,24]

Cognitive outcomes

The Symbol Digit Modalities Test (SDMT) is a neuropsychological test used to measure processing speed or efficiency in patients with MS, commonly used to determine the efficacy of treatments.[25] The SDMT involves writing symbols in accordance with the target key presented to the patients at the top of the exam page. The key pairs single digits (1–9) with nine different symbols, followed by rows that only contain symbols. Patients are tasked to write or orally report the correct number in the space below. After completing the first 10 items with guidance, patients are given 90 s to complete as many items as possible that follow.[25]

Functional composite measures

Another widely accepted instrument to monitor disease progression is the Multiple Sclerosis Functional Composite (MSFC) measure, which consists of three measured components: Timed 25-Foot Walk, assessing gait; 9-Hole Peg Test, assessing arm and hand function; and the Paced Auditory Serial Addition Test-3 (PASAT-3), assessing cognitive function. A different iteration of the MSFC has been proposed in which the SDMT replaces the PASAT-3, as it is a simpler and shorter test, but recommendations remain to use it as a complementary tool in addition to the MSFC or as a stand-alone test.[20,26]

Patient-reported outcomes

In addition to clinical scales, patient-reported outcome scales can also be used to a limited extent to monitor disease progression through their impact on QoL.[27] The MSQoL-54 measure is a multidimensional QoL scale that combines generic and MS-specific items. Physical health and mental health are derived from two summary scores calculated from a combination of scale scores ranging from 0 to 100, where higher scores indicate better QoL. A positive change from baseline indicates improvement.[27]

Ozanimod and sphingosine-1-phosphate receptor modulators in multiple sclerosis

Sphingosine-1-phosphate receptor (S1PR) modulators are a class of oral therapies used in the treatment of MS. These drugs work by sequestering activated immune cells, preventing them from reaching the CNS and contributing to the formation of new lesions and the reactivation or enlargement of existing lesions.

Sphingosine is the backbone of sphingolipids, a class of lipids that includes the signaling molecule sphingosine-1-phosphate (S1P).[28] When cytokines, immunoglobulins, hormones or trophic factors activate sphingosine kinases, sphingosine is metabolized into S1P.[29] The trafficking of lymphocytes depends on S1PR expression and the gradient of S1P between lymph and lymphoid organs.[30]

S1P can bind five different S1PR subtypes that are involved in numerous and varied cell signaling pathways. S1PR1 is the isoform that is most

Table 1: Comparison of Food and Drug Administration-approved oral sphingosine-1-phosphate receptor modulators[36–39]

Characteristic	Fingolimod[38]	Siponimod[36]	Ozanimod[37]	Ponesimod[39]
Year of FDA approval	2010	2019	2020	2021
FDA indication	RMS (≥10 years)	RMS (adults)	RMS (adults)	RMS (adults)
S1PR specificity	S1PR1,3,4,5	S1PR1,5	S1PR1,5	S1PR1
Daily dose	0.5 mg	1–2 mg	0.92 mg	20 mg
Half life	6–9 days	30 h	21 h	33 h
Time to lymphocyte reconstitution	1–2 months	<1 month	1–3 months	1–2 weeks
First-dose observation requirements	Required for all patients	Required only for select patients at cardiac risk	Not required	Required only for select patients at cardiac risk
ARR (versus comparator)	0.16 versus 0.33–0.40 (placebo/IFN β-1a)	0.20 versus 0.32 (placebo)	0.17–0.18 versus 0.28–0.35 (IFN β-1a)	0.20 versus 0.29 (teriflunomide)
Key safety considerations	Cardiac contraindication: QTc ≥500 ms; class Ia/III antiarrhythmics; PML risk	Potential interactions with medications that affect the CYP2C9 system; genetic testing required for appropriate dosing	Severe untreated sleep apnea; MAOI use contraindicated	—

ARR = annualized relapse rate; FDA = Food and Drug Administration; IFN β-1a = interferon beta-1a; MAOI = monoamine oxidase inhibitor; PML = progressive multifocal leukoencephalopathy; QTc = corrected QT interval; RMS = relapsing multiple sclerosis; S1PR = sphingosine-1-phosphate receptor.

relevant to the treatment of MS. Through S1PR1, S1P elicits egress of lymphocytes into the blood. The S1PR modulators vary in selectivity, but all act as functional antagonists of S1PR1 by inducing prolonged internalization and degradation of the receptor.[31] This action prevents S1P from activating the receptor and reduces the migration of immune cells to the CNS. These drugs have shown selectivity for pathogenic lymphocyte subsets, and it has been suggested that they exert their effects without impairing the immune system's ability to respond to infections.[32–34]

Fingolimod was the first S1PR modulator approved for the treatment of MS and has activity at S1PR1, S1PR3, S1PR4 and S1PR5. Three other S1PR modulators have received regulatory approval for the treatment of MS. Ponesimod is selective for S1PR1, whereas ozanimod and siponimod target both S1PR1 and S1PR5. The selectivity for certain receptors contributes to fewer side effects.[29] Of these four medications, only fingolimod requires all patients to undergo first-dose monitoring due to the risk of bradycardia.[35] Siponimod is unique in that CYP2C9 genotype testing must be performed prior to treatment initiation to determine dosing; it is contraindicated in patients with the CYP2C9*3/*3 genotype.[36]

Ozanimod is a once-daily oral S1PR modulator with a recommended dose of 0.92 mg.[37] Treatment is initiated using a 7-day titration to the maintenance dose, but there is no required first-dose monitoring. Following treatment discontinuation, lymphocyte reconstitution occurs within approximately 1–3 months with ozanimod, 1–2 months with fingolimod, <1 month with siponimod and 1–2 weeks with ponesimod.[36–39]

Table 1 summarizes key characteristics of the four FDA-approved S1PR modulators.[36–39]

Oral S1PR modulators as a class require safety monitoring, including pretreatment electrocardiogram (ECG), bloodwork, ophthalmic evaluation, blood pressure monitoring and periodic dermatologic assessments.[36–39] Safety considerations shared across the class include infection risk, bradyarrhythmia and atrioventricular (AV) conduction delays, macular edema, liver injury, hypertension, respiratory effects, cutaneous malignancy and potential worsening of disease activity after discontinuation.[36–39]

Clinical trials with ozanimod

Findings from the initial phase 1 study of ozanimod in healthy human subjects, published in 2017, demonstrated that ozanimod was well tolerated and produced selective effects on lymphocyte subtypes believed to be involved in the immunopathologic process of RMS.[32] As a result, further clinical research was pursued to investigate ozanimod as a potential treatment for chronic inflammatory diseases. The following sections present key safety and efficacy findings from the pivotal phase 2 and phase 3 clinical trials of ozanimod.

Phase 2 trials

RADIANCE Part A

RADIANCE Part A (Efficacy and Safety Study of Ozanimod (RPC1063) in Relapsing Multiple Sclerosis Patients (RADIANCE); ClinicalTrials.gov identifier: NCT01628393) was a phase 2, multicenter, randomized, double-blind, placebo-controlled study that evaluated ozanimod in patients with RMS over a 24-week period. A total of 258 patients between the ages of 18 and 55 years were enrolled and randomized into one of the following groups: ozanimod 0.5 mg, ozanimod 1 mg or placebo.[40]

The primary endpoint of this trial was the cumulative GdE lesions on MRI between weeks 12 and 24. Both ozanimod groups showed a reduction in total GdE lesions, with a reduction of 84% being observed for the 0.5 mg group and a reduction of 89% for the 1 mg group. Reductions in new or enlarging T2 lesions were also observed among patients receiving ozanimod compared with the placebo group. While ARR did not differ significantly between the placebo and ozanimod groups, a *post hoc* analysis showed that 83% and 87% of patients receiving ozanimod 0.5 mg and 1 mg, respectively, were relapse-free during the 24-week treatment, in contrast to 77% of patients receiving placebo.[40]

Ozanimod was generally well tolerated throughout the study, with 252 of the 258 enrolled participants completing the trial. Of the participants who did not complete the study, none discontinued treatment due to adverse events. Most treatment-emergent adverse events (TEAEs) were mild to moderate, with the most common being nasopharyngitis, headache, urinary tract infection (UTI) and orthostatic hypotension. The study reported no notable cardiovascular, pulmonary, ophthalmic,

infectious or malignancy-related TEAEs, and no incidence of macular edema. Of the four observed severe TEAEs, three were considered unrelated to treatment. Elevations in alanine aminotransferase (ALT) >3 × the upper limit of normal were observed in three patients. All cases were mild, isolated and resolved without intervention. In addition, expected reductions in absolute lymphocyte counts were observed.[40]

RADIANCE Part A extension

Participants completing the 24-week phase 2 trial were eligible to enroll in a masked extension study in which patients previously receiving placebo were re-randomized to ozanimod (0.5 mg or 1 mg), while patients previously receiving ozanimod continued their assigned dose. The extension phase demonstrated high retention rates, with 249 out of the 252 eligible patients entering the 2-year extension.[41]

Across the extension period, ozanimod maintained a favorable safety profile, with no evidence of increasing adverse events over time. TEAEs were observed in 77% of all patients, with the most common being nasopharyngitis, upper respiratory tract infection and increased ALT, consistent with the findings from the Part A study.[40] Serious TEAEs occurred in fewer than 10% of patients in both treatment groups, and none were considered related to ozanimod. Four patients discontinued per protocol due to elevations in ALT, although all cases resolved after drug discontinuation. There was no evidence of macular edema or malignancy.[41]

Efficacy outcomes were sustained throughout the extension, as evidenced by the low levels of MRI lesion activity and low unadjusted ARR. Participants initially receiving placebo showed a decrease in the number of GdE MRI lesions following transition to ozanimod, with results being sustained throughout the trial. Although the study was not designed to test dose dependency, the 1 mg dose of ozanimod showed greater efficacy across both MRI and clinical disease measures.[41]

Phase 3 trials

SUNBEAM and RADIANCE Part B

Two pivotal phase 3 trials, SUNBEAM (Study of Ozanimod [RPC1063] in Relapsing Multiple Sclerosis [MS] [SUNBEAM]; ClinicalTrials.gov identifier: NCT02294058) and RADIANCE Part B (Efficacy and Safety Study of Ozanimod in Relapsing Multiple Sclerosis [RADIANCE]; ClinicalTrials.gov identifier: NCT02047734), evaluated the safety and efficacy of ozanimod by comparing it with intramuscular interferon beta-1a (IFN β-1a). Both trials were multicenter, randomized, double-blind, double-dummy trials with similar designs.[42,43] The two trials largely adopted eligibility criteria similar to those used in the earlier RADIANCE Part A study, enrolling patients with RMS and comparable baseline disease activity. The main difference between the two trials was study duration, with SUNBEAM lasting 12 months and RADIANCE Part B lasting 24 months.[42,43]

Patients were randomized to one of three treatment groups: ozanimod 1 mg, ozanimod 0.5 mg or IFN β-1a. To maintain blinding, all patients received a daily pill and a weekly injection, with one administered as a placebo. As with RADIANCE Part A, the primary efficacy endpoint of both phase 3 trials was ARR, with key secondary endpoints including MRI lesion activity and measures of disability progression, as assessed by EDSS.[42,43]

Across both trials, ozanimod was associated with a significantly lower adjusted ARR compared with IFN β-1a, as well as fewer new or enlarging T2 lesions and GdE lesions. Ozanimod treatment also resulted in less brain volume loss (including whole brain volume, cortical gray matter volume and thalamic volume) than IFN β-1a, suggesting potential protection against structural changes associated with MS progression. Additionally, ozanimod appeared to provide modest benefits in cognitive processing speed compared with IFN β-1a, as evidenced by the greater percentage of patients previously receiving ozanimod who experienced improved SDMT scores at 6-month and 12-month time points.[44] In a pooled analysis of the two trials, ozanimod showed no evidence of risk reduction in time to CDP as compared with IFN β-1a, although neither study was designed to detect significant differences in this endpoint.[41] Overall, ozanimod resulted in greater efficacy on clinically meaningful measures of disease activity, such as MRI and ARR, compared with treatment with IFN β-1a.[42,43]

Ozanimod continued to present a favorable safety profile in both trials, generally consistent with findings from the earlier RADIANCE Part A study.[40,41] Most TEAEs across the IFN β-1a and ozanimod groups were mild or moderate in severity, and the incidence of serious TEAEs was similar across groups. Ozanimod, however, resulted in a lower incidence of TEAEs leading to discontinuation compared with IFN β-1a. Collectively, these findings indicate that ozanimod is both effective and generally well tolerated in patients with RMS.[42,43]

DAYBREAK

The DAYBREAK (A Multi-Site, Open-Label Extension Trial of Oral RPC1063 in Relapsing Multiple Sclerosis; ClinicalTrials.gov identifier: NCT02576717) study was a phase 3 open-label, single-arm extension study designed to evaluate the long-term safety and efficacy of ozanimod in patients who completed one of the previously mentioned parent studies: RADIANCE Part A, SUNBEAM, and RADIANCE Part B. In total, 2,494 participants were enrolled in DAYBREAK, with a mean exposure duration of approximately 60.9 months.[45]

Overall, DAYBREAK demonstrated a favorable long-term safety and tolerability profile that was consistent with the findings from the previous clinical trials. Most TEAEs were mild or moderate in severity. Serious TEAEs and discontinuations due to adverse events remained infrequent with prolonged follow-up. Infections were common but mostly non-serious. One case of progressive multifocal leukoencephalopathy (PML) was reported after approximately 4 years of treatment, with partial neurologic recovery following discontinuation of ozanimod. Macular edema and malignancies, including basal cell carcinomas and isolated cases of breast cancer, occurred at low incidence, most often occurring in patients with pre-existing risk factors.[45]

The long-term efficacy outcomes from DAYBREAK suggested sustained clinical and radiological disease control with ozanimod. The adjusted ARR remained low (0.098), and MRI measures demonstrated low rates of new or enlarging T2 lesions and GdE lesions. Overall, 69.1% of patients remained relapse-free through extended follow-up, and 84.8% of participants remained free from 6-month CDP at study completion.[45]

Collectively, the DAYBREAK study supports the long-term safety and durability of ozanimod, reinforcing findings from earlier clinical trials and providing evidence of sustained benefit from continued treatment.

Summary and further evidence

The key findings from the clinical trials discussed above are summarized in *Table 2*.

Table 2: Summary of key clinical trial designs and outcomes for ozanimod in multiple sclerosis[40,42,43,45]

	RADIANCE Part A[40]	SUNBEAM[42]	RADIANCE Part B[43]	DAYBREAK[45]
Phase	Phase 2	Phase 3	Phase 3	Phase 3
Study duration	24 weeks	≥12 months	24 months	Up to 6.8 years
Comparator	Placebo	IFN β-1a	IFN β-1a	—
Primary endpoint	Cumulative GdE lesions at weeks 12–24	ARR during treatment period	ARR during treatment period	Long-term safety
ARR (95% CI)				
Ozanimod 1.0 mg*	0.24 (0.10–0.60)	0.18 (0.14–0.24)	0.17 (0.14–0.21)	0.098 (0.082–0.117)
Ozanimod 0.5 mg	0.35 (0.20–0.80)	0.24 (0.19–0.31)	0.22 (0.18–0.26)	—
Comparator	0.5 (0.2–1.2)	0.35 (0.28–0.44)	0.22 (0.18–0.26)	—
MRI disease activity	Reduced GdE lesions by 84–89% and T2 lesions versus placebo	Reduced GdE and T2 lesions versus IFN β-1a	Reduced GdE and T2 lesions versus IFN β-1a	Low and stable new/enlarging GdE and T2 lesions through extended follow-up
Disability progression	Not a key endpoint; not reported in detail	No significant difference versus IFN β-1a	No significant difference versus IFN β-1a	At end of study: 82.8% and 84.8% free from 3-month and 6-month CDP, respectively

**For consistency with the earlier trials, all ozanimod doses in this table are presented as the HCl salt form (e.g. 1.0 mg, 0.5 mg), which are equivalent to the active compound doses of 0.92 mg and 0.46 mg, respectively.*
ARR = annualized relapse rate; CDP = confirmed disability progression; CI = confidence interval; GdE = gadolinium-enhancing; IFN β-1a = interferon beta-1a; MRI = magnetic resonance imaging.

Emerging real-world evidence has further supported the effectiveness of ozanimod in routine clinical practice. In a prospective observational study using the Brief International Cognitive Assessment for Multiple Sclerosis, 69.7% of participants demonstrated improvements in cognitive processing speed, with a mean increase in SDMT z-scores of 0.34 following treatment with ozanimod. These findings complement the cognitive benefits observed in the phase 3 clinical trials and suggest that the effects of ozanimod may extend beyond relapse control and MRI disease activity.[46]

Safety and patient considerations

Considerations prior to starting ozanimod

Prior to starting ozanimod, several assessments must be completed to ensure patient safety. A complete blood count and liver enzymes should be obtained before initiation and monitored throughout treatment. Ozanimod causes a mean peripheral blood lymphocyte count reduction to 45% of baseline and should not be started until active infections have been resolved. If liver injury is suspected during treatment, ozanimod should be discontinued. An ophthalmic assessment to obtain a baseline evaluation of the fundus must be completed and repeated periodically throughout treatment, or any time there is a change in vision. ECG should be checked at baseline to assess for pre-existing abnormalities. Cardiology consultation is recommended for patients with cardiac conduction abnormalities or for patients concurrently taking other medications that slow heart rate. Skin examination is recommended at baseline and periodically throughout treatment. If any live attenuated vaccines are needed, these must be received at least 1 month prior to starting ozanimod, as they cannot be received during ozanimod use and until 3 months following ozanimod cessation. If the patient does not have a confirmed history of chickenpox or a full course of vaccination against varicella zoster virus (VZV), the patient should be tested for VZV antibodies and vaccinated prior to starting treatment if antibody-negative.[37]

Concomitant medications and contraindications

Possible additive immunosuppressant effects should be considered in patients taking antineoplastic, non-corticosteroid immunosuppressive or immune-modulating therapies, or if there is a history of prior use. Additionally, consultation with cardiology is recommended for patients who take drugs that could slow heart rate or AV conduction.[37]

Some metabolites of ozanimod are inhibitors of monoamine oxidases (MAOs), with a 1000-fold selectivity for MAO-B over MAO-A. No clinical studies have evaluated the interaction of ozanimod with MAO inhibitors (MAOIs), and co-administration of ozanimod with MAOIs is contraindicated. Concomitant use with serotonergic antidepressants is permitted.[37] During the DAYBREAK trial, 12.1% of participants used concomitant selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors, and no TEAEs potentially related to serotonin accumulation were reported, likely due to the selectivity of ozanimod metabolites for MAO-B, which plays a lesser role in metabolism than MAO-A.[47]

Patients who have severe hepatic impairment or severe, untreated sleep apnea should not take ozanimod. Unless the patient has a pacemaker, patients with Mobitz type 2 second-degree or third-degree AV block, sick sinus syndrome or sinoatrial block should not take ozanimod. Additionally, ozanimod is contraindicated in patients who have experienced myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization or class III or IV heart failure within 6 months of treatment initiation.[37]

Pregnancy

Pregnancy should be avoided while on or within 3 months of taking ozanimod. In animal studies, ozanimod produced adverse effects on development, including embryolethality.[37] Clinical trials did not include patients who were pregnant, and participants who became pregnant were discontinued from treatment.[37] One study evaluated pregnancy outcomes in patients who became pregnant while participating in any ozanimod clinical trial. Across the 78 pregnancies that occurred, the study found no increased incidence of spontaneous abortion, preterm birth or congenital abnormalities compared with expected ranges in the general population.[48] However, since no patients followed in the study had been exposed to ozanimod past the first trimester, the safety of ozanimod in later pregnancy could not be assessed. Patients who become pregnant while taking ozanimod may join a pregnancy exposure registry that monitors pregnancy outcomes in patients exposed to ozanimod during pregnancy.[49]

Specific patient populations

The safety and efficacy of ozanimod have not been established in pediatric patients. Clinical studies also included insufficient numbers of patients aged ≥65 to determine whether treatment response differs from that in younger patients. Although no clinically significant differences in the pharmacokinetics of ozanimod were observed based on age, elderly patients should be monitored closely for cardiac and hepatic adverse reactions. In patients with mild to moderate hepatic impairment, the dosing schedule should be adjusted from daily to every other day.[37]

Adverse reactions

Common adverse reactions to ozanimod include upper respiratory infection, hepatic transaminase elevation, orthostatic hypotension, UTI, back pain and hypertension. While most adverse reactions observed in clinical trials were mild to moderate in severity, more serious adverse reactions that patients may experience include PML, bradyarrhythmia and AV conduction delays, liver injury, fetal harm, decreased pulmonary function, macular edema, cutaneous malignancies and posterior reversible encephalopathy syndrome.[37]

Risk of rebound following treatment discontinuation

Disease reactivation, or rebound, following treatment discontinuation has been reported with certain DMTs for MS, most notably fingolimod.[50] However, an exploratory analysis from the DAYBREAK open-label extension study found a low incidence of relapse following ozanimod discontinuation. Among 1,679 participants included in the analysis, 55 patients (3.3%) experienced a relapse within 90 days of permanent treatment discontinuation, with only one relapse classified as severe. No cases of a rebound effect were observed.[51] These findings suggest that, while post-discontinuation disease activity may occur, severe rebound following ozanimod discontinuation appears to be uncommon.

Practical considerations

While clinical trials may assess the safety and efficacy of DMTs, real-world treatment decisions are also influenced by factors that affect access, adherence and patient preference. Patients can face significant barriers in accessing and adhering to their DMT treatments, with one of the most significant barriers being high out-of-pocket costs.[52,53] A conjoint analysis estimating the preferences of patients with MS for various DMTs found out-of-pocket cost to be the most influential attribute, weighted above mode of administration, adverse events and treatment efficacy.[54] When evaluating the annual healthcare costs to avoid relapse, ozanimod demonstrates lower incremental costs and greater annual cost savings compared with fingolimod and IFN β-1a, suggesting ozanimod may offer a favorable cost-effective profile compared with other DMTs.[52]

Treatment delivery and frequency may also play a significant role in patient preference for and adherence to DMTs. A questionnaire of patients with RRMS found that 93% preferred oral DMTs compared with injectables when treatment frequency and side effects were held constant, and that preferences for oral therapies outweighed concerns about mild side effects.[54] Similarly, another study found that patients preferred oral DMTs compared with all injected routes and frequencies.[55] These preferences are reflected in the data surrounding DMT adherence, with studies consistently reporting higher treatment adherence in patients taking oral treatments compared with those treated with injectables.[56–58]

Treatment preference, however, remains highly personal and can differ from individual to individual. For example, a survey of risk tolerance to MS treatments found that several factors affected risk tolerance, including sex, age, level of disability and current DMT.[59] Participants completed a questionnaire on tolerance to hypothetical MS treatments with various associated real-world risks, including skin rash, infection, kidney injury, thyroid injury, liver injury and PML. The study found that men, younger individuals and individuals with greater disability reported a higher risk tolerance to all risk scenarios presented. Women, on the other hand, consistently reported a 2–20× lower risk tolerance compared with men.[59]

Discussion

With more than 20 DMTs approved for MS, each medication must offer a unique balance of efficacy, safety and tolerability to justify its place in the current treatment landscape. While other medication classes, such as the anti-CD20 monoclonal antibody therapies, are more commonly used in patients with MS, S1PR modulators remain the only highly effective once-daily oral option.[60] Within this class, ozanimod has emerged as a valuable treatment option due to its selective S1PR activity, balanced pharmacokinetic profile and favorable safety and tolerability characteristics, which include a low incidence of cardiac and ocular complications.

Although the pivotal clinical trials established the efficacy and safety of ozanimod, several important limitations should be considered when interpreting the data. Most notably, the phase 3 studies compared ozanimod with IFN β-1a, which is no longer among the most commonly used DMTs for many patients with MS.[61,62] As a result, the findings may be less generalizable and do not fully establish ozanimod's place relative to therapies more commonly used in current clinical practice, such as anti-CD20 monoclonal antibodies.

While long-term extension studies continue to support a favorable safety profile for ozanimod, additional real-world follow-up remains important to further characterize its long-term safety. Pregnancy data, in particular, remain limited. Although current evidence reveals no clear safety signal, the limited number of reported pregnancies and the lack of exposure beyond the first trimester leave the safety of ozanimod during pregnancy largely undefined.[48] On-going pregnancy registries and observational studies will be important to better characterize pregnancy outcomes and guide the treatment of patients of childbearing potential.

Overall, while ozanimod provides a well-balanced treatment option for patients seeking an effective once-daily oral medication, additional longitudinal real-world and comparative studies are needed to better characterize treatment persistence, disability progression, cognitive outcomes, pregnancy outcomes and long-term safety of ozanimod relative to contemporary DMTs. Further research on biomarkers capable of predicting response to DMTs may also support more individualized treatment selection and help identify patients most likely to benefit from ozanimod.

Conclusion

Ozanimod represents an important addition to the treatment landscape for RMS by providing an effective once-daily oral therapy with a favorable balance of efficacy, safety and tolerability. As long-term and real-world evidence continues to emerge, additional comparative studies will further define its optimal role among contemporary DMTs and help identify the patients most likely to benefit from treatment. ❑

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